Remarks

Introductory Comments:

Claims 1-4 and 9 have been examined in the Office Action dated 26 July 1994 (Paper No. 8), that Action having been made final. Under the subject Office Action, the Examiner maintains the requirement to review the application for typographical and grammatical errors as set forth in the previous Office Action (Paper No. 5, 19 October 1993). Also by the subject Action, the specification is objected to under 35 U.S.C. § 112, first paragraph, as allegedly not providing an enabling disclosure for the invention as claimed. Further, claim 4 stands rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification. Finally, claims 1-3 and 9 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure is allegedly enabling for claims limited to the $KGF_{des1-23}$ fragment. The subject requirement, objection and rejections are believed to be overcome in light of the amendments and remarks, and applicants respectfully request the Examiner's withdrawal thereof.

Amendments:

By the present response, minor typographical errors appearing in the specification have been corrected. Further, non-elected claims 5-8 and 10-23 have been cancelled, without prejudice, and claims 1 and 9 have been amended to particularly recite the $KGF_{des1-23}$ fragment of the present invention. At the same time, new dependent claims 24-35 have been added to further recite the subject invention. No new matter has been entered by the present amendments. Before responding directly to the various issues raised in the action, the amendments to the

pending claims, and the new claims are briefly summarized below in order to assure a better understanding thereof.

Independent claim 1, as amended, is directed toward the keratinocyte growth factor fragment having a least a 2-fold increase in mitogenic activity as compared to mature, recombinant, full-length keratinocyte growth factor (KGF). The fragment lacks a sequence comprising the first 23 N-terminal amino acid residues of the mature, full-length KGF.

Independent claim 9, as amended, is directed toward a therapeutic composition comprising a KGF fragment as described above in regard to claim 1, and a pharmaceutically acceptable carrier.

New dependent claim 24 is directed toward a KGF fragment, wherein that fragment comprises an amino acid sequence corresponding to residues 55 to 194 of Figure 1 [SEQ ID NO: 1]. Support for this claim may be found, *inter alia*, at page 6, lines 7-18; page 11. lines 23-27; and in Fig. 1, [SEQ ID NO: 1].

New dependent claim 25 is directed toward analogs of the KGF fragment of claim 24, wherein the analog has at least one conservative substitution of an amino acid with a structurally related amino acid and further wherein the analog exhibits the biological activity of the KGF fragment. Support for this claim may be found, *inter alia*, at page 6, lines 19-29 to page 7, lines 1-2; and page 11, lines 9-18.

New dependent claim 26 is directed toward the analogs of claim 25, wherein the conservative substitutions comprise isolated amino acid replacements in the fragment that are selected from the group consisting of a leucine with an isoleucine, a leucine with a valine, an aspartic acid with a glutamic acid and a threonine with a serine. Verbatim support for this claim may be found at page 7, lines 2-7.

New claim 27 is also directed toward analogs of claim 24, wherein at least one cysteine residue has been substituted by another amino acid and further wherein those analogs exhibit the biological activity of the subject KGF fragment. New claim 28 is directed toward the analogs of claim 27 wherein the cysteine residue is replaced with serine or threonine. Support for these claims may be found, *inter alia*, at page 6, line 19 through page 7, line 7.

New dependent claims 29-33 are directed toward therapeutic compositions comprising the KGF fragments and/or analogs of claims 24-28. Support for these claims may be found, *inter alia*, at page 9, line 28 through page 10, line 9; page 13, lines 6-10; and at the pages indicated above as providing support for the molecules of claims 24-28.

Turning now to the Action, applicants respond to the substantive portions thereof as follows.

The Requirement re: Typographical and Grammatical Errors:

By the pending Office Action, the Examiner has maintained the requirement to review the application for typographical and grammatical errors. Applicants have so done. Accordingly, this basis for rejection has been overcome.

The Objection to the Specification and Rejection of Claim 4 under 35 U.S.C. § 112, First Paragraph:

By the present Action, the Examiner has also maintained the objection to the specification under 35 U.S.C. § 112, first paragraph, as set forth at pp. 5-6 of the previous Office Action (Paper No. 5). The Examiner alleges that the specification fails to provide an enabling disclosure Further, claim 4 remains rejected under 35 U.S.C. § 112, first paragraph for the reasons

set forth in the objection to the specification. In this regard, the Examiner asserts that:

> "The specification fails to teach a skilled artisan how to make and use KGF fragments or analogs exhibiting decreased cytotoxicity. Specifically, the specification provides no evidence that the keratinocyte growth factor (KGF) fragment (such as $KGF_{des1-23}$) exhibits decreased cytotoxicity as compared to the mature, full-length KGF. The specification does provide evidence that $KGF_{des1-23}$ has increased mitogenic activity. However, it does not immediately follow from this data that $KGF_{des1-23}$ has decreased cytotoxicity. In fact, a skilled artisan might expect a more biologically active molecule to be more cytotoxic, in that an organism may not be able to support dramatically increased cell growth and division. In the absence of any guidance in the specification regarding decreased cytotoxicity of KGF fragments, a skilled artisan would be unable to make and use the invention as claimed, for example, claim 4."

The Examiner goes on to assert that "[c]laim 4 is not limited to $KGF_{des1-23}$; thus, arguments pertaining only to $KGF_{des1-23}$ are not persuasive to establish enablement for the entire scope of the claims." Although the Examiner acknowledges that applicants have taught how to make $KGF_{des1-23}$, (see page 3 of the Office Action), the Examiner argues that there "is no evidence" that the subject fragment possess decreased cytotoxicity. The Examiner also asserts that applicants' reliance on the disclosure of page 15, lines 7-13; page 37, lines 3-5; and Fig. 4 of the specification to provide evidence of decreased cytotoxicity is insufficient, as, "there is no indication that the difference in toxic effects between $KGF_{des1-23}$ and KGF_{163} is statistically significant." Further, the Examiner contends that "there is no indication of sample size or controls" which a "skilled artisan would require in order to use the invention"; and, finally, the

Examiner claims that applicants "[have] not indicated exactly which data presented in Fig. 4 speak to decreased cytotoxicity." The above grounds of objection/rejection are believed to be overcome or are otherwise traversed for the following reasons.

Initially, applicants wish to draw the Examiner's attention to amended claim 1 (and, accordingly, dependent claim 4) which now recites the $KGF_{des1-23}$ fragment. In light of the subject amendment, the Examiner's assertion that "arguments pertaining only to that fragment are not persuasive to establish enablement for the entire scope of claim 4" has been obviated.

Further, applicants note that the Federal Circuit has determined that "[e]nablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive, and is determined as of the filing date of the patent application.... Furthermore, a patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) (citations omitted).

Thus, applicants respectfully submit that their responsibility under 35 U.S.C. § 112, first paragraph, is to "enable any person skilled in the art...to make and use" the invention as recited in claim 4. As helpfully acknowledged by the Examiner (*see, e.g.*, page 3 of the present Office Action), applicants have clearly met this charge, as they <u>have taught how to make the $KGF_{des1-23}$ fragment</u>. As applicants have already noted (see, e.g., Paper No. 7, dated 19 April 1994), the specification describes several methods of how to prepare the $KGF_{des1-23}$ fragment, *see for example*, the disclosure of page 11, lines 5-8; and page 11, line 19 through page 12, line 22. Further, applicants <u>have taught how to use the $KGF_{des1-23}$ fragment</u>, *see for example*, the

disclosure of page 2, lines 22-26; and page 13, lines 6-10. Therefore, applicants' specification clearly enables a person skilled in the art to make and use the $KGF_{des1-23}$ fragment in accordance with Section 112, first paragraph.

In response to the Examiner's allegations that there "is no evidence" that the $KGF_{des1-23}$ fragment possesses decreased cytotoxicity, and further that the data "fail to show decreased cytotoxicity", applicants respectfully draw the Examiner's attention to the disclosure of page 15, lines 7-13 wherein it is stated that the $KGF_{des1-23}$ molecule, *at high concentrations*, does not have a toxic effect (has decreased cytotoxicity) toward keratinocytes in contrast to that observed for the KGF_{163} molecule. In this regard, applicants submit that the term "cytotoxicity" must be read to have its ordinary meaning (e.g., toxic to cells). By employing the bioactivity assay as described in the specification at page 38, line 1 through page 39, line 18, the novel features of KGF fragments (e.g., increased mitogenic activity and decreased cytotoxicity as compared to full-length KGF) recited in claim 4 may be readily determined by one of ordinary skill in the art.

In this manner, referring to the data presented by Fig. 4, it is clear that the full-length KGF_{163} molecule (denoted as "long form") exhibits a cytotoxic effect at high concentrations. Although KGF_{163} shows an optimum level of bioactivity at a concentration of about 8 ng/ml, at concentrations greater than 8 ng/ml (e.g., about 8.5 to about 21 ng/ml), the KGF_{163} molecule not only shows decreased bioactivity, but also exhibits a clear cytotoxic effect as the cell density of Balb/Mk cells exposed to those concentrations decreases sharply in a linear relation to increased fragment concentration. Conversely, the $KGF_{des1-23}$ fragment (denoted as "short form") does not exhibit a cytotoxic effect at high concentrations (see Fig. 4). Specifically, at

$KGF_{des1-23}$ fragment concentrations ranging from about 0.1 to about 21 ng/ml, the bioactivity of the $KGF_{des1-23}$ fragment remains high and no cytotoxic effect is exhibited over the entire fragment concentration range (e.g., the cell density of the Balb/Mf cells remains constant in relation to increased fragment concentration). In short, the data demonstrate that the KGF_{163} molecule at varying concentrations (e.g., between about 0.1 ng/ml and 7.5 ng/ml, and from about 8.5 ng/ml to greater than 21 ng/ml) lacks stability, whereas the KGFdes1-23 fragment is very stable, especially between about 0.1 to about 21 ng/ml.

Thus, it is respectfully submitted that, in light of the disclosure regarding the KGF bioactivity assay using Balb/Mk cells (see page 38, line 1 through page 39, line 18), and of the data depicted by Fig. 4, applicants have clearly provided a skilled artisan with the requisite enabling disclosure necessary to make and use a $KGF_{des1-23}$ fragment having increased mitogenicity and decreased cytotoxicity as recited in claim 4.

Furthermore, in regard to the Examiner's maintenance of the allegation that the specification and claim 4 are not enabled, as,

> "it does not immediately follow from this data that $KGF_{des1-23}$ has decreased cytotoxicity. In fact, a skilled artisan might expect a more biologically active molecule to be more cytotoxic, in that an organism may not be able to support dramatically increased cell growth and division",

applicants wish to remind the Examiner that, in making a rejection for lack of enablement, it is incumbent upon the Examiner to explain why the objective truth of the disclosure is doubted and to back up such assertions with acceptable objective evidence or reasoning in support thereof. See, 37 CFR 1.71(c); and *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed Cir 1986). How such a teaching is set forth, either by

the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971)).

In this regard, applicants note that no reference has been cited by the Examiner in support of the contention that "more biologically active molecules are more cytotoxic". If the Examiner has facts within her personal knowledge to support such assertions, applicants respectfully request that she provide specific data in support thereof in an affidavit pursuant to 37 C.F.R. §1.107(b). Absent such evidentiary showing, applicants submit that the Examiner's section 112, first paragraph objection to the specification and rejection of claim 4 are improper as the Office Action has failed to establish a lack of enablement thereof.

Reconsideration and withdrawal of the objection to the specification and the rejection of claim 4, both grounded under 35 U.S.C. § 112, first paragraph, is therefore respectfully requested for the foregoing reasons and in light of the amendments to the claims.

The Rejection of Claims 1-3 and 9 under 35 U.S.C. § 112, First Paragraph:

The Examiner next maintained the rejection of claims 1-3 and 9 under 35 U.S.C. §112, first paragraph, for reasons as set forth in the previous Office Action (Paper No. 5). More particularly, the Examiner continues in the assertion that the rejected claims are non-enabled, as, "the disclosure is enabling

only for claims limited to $KGF_{des1-23}$" as per M.P.E.P §§ 706.03(n) and 706.03(z)." The Examiner asserts that

> "The specification provides evidence that $KGF_{des1-23}$ exhibits increased mitogenic activity as compared to mature, full-length KGF. However, no other KGF fragments have been demonstrated to exhibit the increased mitogenic activity. In fact, other researchers have obtained KGF fragments lacking N-terminal sequences both shorter and longer than the disclosed $KGF_{des1-23}$, and have found that these KGF fragments display unchanged or lower mitogenic activity (see Ron et al., reference CC of record). This evidence speaks to the high degree of unpredictability inherent in truncated growth factors. Thus, undue experimentation would be required by a skilled artisan to evaluate all non-exemplified KGF fragments for increased mitogenic activity...".

The Examiner further asserts that

> "No analogs of KGF fragments have been fully described or analyzed for biological activity. It is well known in the art that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within the active site or alters the overall conformation of the protein molecule. Thus, undue experimentation would be required by a skilled artisan to evaluate all non-exemplified analogs of KGF fragments that have increased mitogenic activity."

In response, applicants draw the Examiner's attention to the amendments to claims 1 and 9 which have been tendered herewith. By the subject amendments, claims 1 and 9 (and, accordingly, dependent claims 2-3) are now drawn to the $KGF_{des1-23}$ fragments which the Examiner has recognized as being sufficiently enabled (see the Office Action, Paper No. 8, page 4). Accordingly, in light of the above-described amendments, reconsideration and withdrawal of the rejection of claims 1-3 and

9 grounded under 35 U.S.C. § 112, first paragraph, is respectfully requested.

In regard to the Examiner's maintenance of the section 112, first paragraph rejection toward the KGF analogs (previously recited in claims 1-3 and 9), applicants draw the Examiner's attention to new claims 25-28 wherein the subject analogs have been recited with greater particularity. Applicants submit that the analogs of new claims 25-28 are clearly enabled by the present application for the following reasons.

Initially, applicants note that the first paragraph of 35 U.S.C. § 112 merely requires that the scope of protection sought in a claim bear a *reasonable correlation* to the scope of enablement provided by the specification. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), (citing *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970)), (emphasis added by applicants). As helpfully acknowledged by the Examiner in the instant Office Action (Paper No. 8), applicants have defined and taught how to make and use the fragment $KGF_{des\text{-}123}$, and further have taught how to make analogs thereof using amino acid substitutions, deletions, and insertions that are within the skill of art (see Paper No. 8, page 5). Accordingly, the novel KGF analogs (formerly recited by claims 1-3 and 9, and now recited by new claims 25-28) are adequately supported by the specification, and it is clear that applicants have complied with the *reasonable correlation* requirements of Section 112, first paragraph.

Thus, it is submitted that the Examiner's chief concerns under the first paragraph of Section 112 regarding the recited KGF analogs seems to be that "the specification provides only a single working example: $KGF_{des1\text{-}23}$", that "there is no reasonable expectation that such analogs would have the required activity recited in the claims", and therefore, "undue experimentation would be required by a skilled artisan to

evaluate all non-exemplified KGF fragments for increased mitogenic activity". See Paper No. 8, page 5; and Paper No. 5, page 7. To respond, applicants wish to remind the Examiner that under 35 U.S.C. §112, first paragraph, "*nothing more than objective enablement is required*, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), (citing *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971)), (emphasis added by applicants). The Examiner is also reminded that there is no requirement under the Patent Laws which requires applicants to provide working examples to support the claims. *In re Robbins*, 166 USPQ 552 (CCPA 1970).

Applicants note that under the invention, analogs of the $KGF_{des1-23}$ fragment are defined as including

> "amino acid insertions, deletions, or substitutions in the relevant molecule that do not substantially affect its properties. The $KGF_{des1-23}$ analog herein retains at least the 2-fold increase, preferably, the 7-fold increase, more preferably, the 7-10 fold increase mitogenic activity as compared to that of $rKGF_{163}$. For example, the analog herein can include conservative amino acid substitutions in the $rKGF_{des1-23}$ molecule." See page 6 of the specification, lines 19-24.

By the specification, conservative amino acid substitutions are defined as including, for example, "those that take place within a family of amino acids that are related in their side chains". See page 6, line 25 through page 7, line 2. In this regard, applicants respectfully remind the Examiner that it is generally accepted in the art that conservative substitutions of an amino acid with a structurally related amino acid, in an area outside of the polypeptide's active site, will not have a major effect on the properties of the polypeptide (*see, e.g.*, page 7 of the specification, lines 2-7).

Further by the specification, analogs of the $KGF_{des1-23}$ molecule are defined to retain the epithelial cell specificity and the at least 2-fold increase in mitogenic activity of that fragment (see page 11, lines 9-11). Such analogs may be provided using methods well known in the art, including post-translationally modified versions of $rKGF_{des1-23}$, for example, those generated by glycosylations, acetylations, or phosphorylations thereof; and further include molecules made by conventional techniques of amino acid substitution, deletion, or addition, for example, by site-directed mutagenesis (see page 11, lines 13-17 of the specification).

Applicants draw the Examiner's attention to the Board's decision in *In re Mark*, 12 USPQ2d 1904 (BOPAI 1989), wherein it was found that only routine experimentation would be needed for one skilled in the art to practice the claimed invention (involving conservative substitutions of cysteine residues) for a given protein. The Board specifically found that

> "[t]he fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity." 12 USPQ2d at 1907.

The same holds true in the instant matter. Applicants note that the analogs as now recited in claims 25-28 may be routinely prepared using amino acid substitutions, deletions, and insertions that are *per se* within the skill of art. Further, the recited analogs may be routinely screened for bioactivity using the methods provided by the specification for increased mitogenic activity. The Examiner is respectfully reminded that satisfaction of the enablement requirement of Section 112 is not

precluded by the necessity for some experimentation such as routine screening. The operative word in this regard is "undue", not "experimentation". See *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Further, applicants note that the metes and bounds of the analogs recited by new claims 25-28 are well delineated by the disclosure noted above, and that the particular examples provided clearly enable a skilled artisan to make and use the subject KGF analogs. It is well settled that applicants need not test all embodiments of their invention in order to meet the requirement of Section 112. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). Accordingly, applicants have clearly met their obligation of objective enablement of the analogs recited by claims 25-28 as per Section 112 through the enabling disclosure and the illustrative examples noted above.

In light of the above-noted new claims drawn toward the KGF analogs of the present invention, those claims finding sufficient support in the specification as originally filed, applicants submit that the Examiner's grounds of rejection under 35 U.S.C. § 112, first paragraph are obviated and clearly overcome.

Conclusion

It is therefore submitted that the invention as now claimed is clearly enabled by the specification as filed, and fully described in such a way as to comport with the requirements of 35 U.S.C. § 112, first paragraph. The Examiner's concurrence by way of an early allowance of the subject claims is therefore earnestly solicited.

The Examiner is requested to direct all further

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